REMARKS

After amending the claims as set forth above, claims 1-5, 8-36, 38 and 44-57 are now pending in this application. Claim 37 is canceled without prejudice or disclaimer and claims 1, 3-5, 8, 9, 18, 20, 30, 32, 33, 35, 38 and 44-50 are amended. Claims 1, 3, 4, 5, 8, 18, 30, 35 and 39 are amended to recite that the pharmaceutical compositions are administered via airway treatment. Support for this amendment is found in the specification on page 1, lines 15-18; page 1, lines 25-27; page 16, lines 24-26; and page 17, lines 26-28 as well as the original claims. The amendments to claims 44-48 and 50 are supported by original claim 14 and the new claims are supported in the original claims and specification. Applicants reserve the right to file the subject matter of any canceled claims or canceled subject matter in one or more continuing applications.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 13, 14, 44-48 and 50

Claims 13, 14, 44-48 and 50 are rejected as allegedly not enabled by the specification because the specification does not provide the description of the structure of such promoters, such as their nucleotide sequences and evidence that the members of a class of such promoter share a common structure. Applicants respectfully traverse this rejection and note that the Examiner states that this rejection might be overcome if evidence can be provided that shows that such mammalian cell specific promoters were sufficiently well known in the art at the time of the present invention.

In response to the Examiner's query, applicants confirm that mammalian cell specific promoters were well known in the prior art to persons skilled in the art at the time of the present invention. The DNA sequences of the promoters have been described in many papers and the sequences published in GenBank. Anyone with reasonable skill in the art could use this information to construct a promoter that would limit expression of a transgene carried by a plasmid, virus, liposome, vector, etc. that was delivered into an organism to either epithelial or smooth muscle cells. For example, in regard to expression in epithelial cells, regulatory elements from the human cytokeratin 18 (K18) gene have been

used to direct epithelial cell-specific expression of genes in lung airways. See Chow *et al., Proc. Natl. Acad. Sci. USA* 94:14695-14700 (1997) **(Exhibit 1)**; Chow et al., *Molecular Therapy* 2:359-367 (2000) **(Exhibit 2)**. The expression cassette includes the first intron, minimal promoter and 2 5'-untranslated regions of the human K18 gene (GenBank Accession Numbers M24842, M19353 and X12799). A second promoter for lung epithelial genes has been described and proposed for use to drive epithelial cell specific expression of transgenes as the human surfactant Protein B promoter in Strayer et al., Am. J. Respir. Cell Mol. Biol. 18:1-11 (1998) **(Exhibit 3)**. The surfactant Protein B promoter was described in Venkatesh et al, *Amer. J. Physiol.* 268:L674-L682 (1995) **(Exhibit 4)**. Additionally, mammalian cell specific promoters continue to be identified and used, such as another promoter that could be used to direct expression of a transgene in airway epithelial cells: the human WNT7b promoter (Weidenfeld et al., *J. Biol. Chem.* 277:21061-21070, (2002)) **(Exhibit 5)**, which drives expression of a signaling molecule. The expression of WNT7b is limited to airway epithelium. The GenBank accession number of the DNA sequence of this promoter is AF456420.

Also the most commonly used promoter to direct expression of a transgene to smooth muscle is the promoter of the alpha-actin gene. The regulatory elements in the alpha-actin gene that limit expression of this gene to smooth muscle were described by Foster *et al., J. Biol. Chem.* 267:11995-12003.(1992) **(Exhibit 6)**. In the paper, detailed instructions are provided that identify the promoter sequence and how to prepare the promoter for fusion to another gene. McGraw *et al. J. Biol. Chem.* 274:32241-32247 (1999) **(Exhibit 7)** used the alpha-actin promoter to direct overexpression of beta2-adrenergic receptors in airway smooth muscle.

Applicants believe that they have provided sufficient evidence to support their position that the mammalian cell specific promoters were well known by persons in the art. Applicant submits that a "patent need not disclose, and preferably omits, what is well known in the art." *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). In view of the above information provided regarding the what is known by persons skilled in the art, it is requested that this rejection be withdrawn.

In regard to the rejection of claims 44-48 and 50 as introducing new matter into the specification, these claims have been amended to recite that these promoters are "mammalian cell specific promoters." It is requested that this rejection be withdrawn.

Claims 1-5, 8-38 and 44-50

Claims 1-5, 8-38 and 44-50 are rejected as allegedly not enabled by the specification because the Examiner alleges that the application is not enabled for the treatment of diseases other than asthma. Applicants respectfully traverse this rejection.

At this time, the claims have been amended to methods that administer the β2AR via airway treatment to airway epithelial cells and/or airway smooth muscle cells. However, there are airway diseases other than asthma that can be treated using the methods of the present invention. For example, any airway disease that can benefit from β2AR-mediated processes in airway cells, such as mucus clearance, production of bronchoactive factors as discussed on pages 6-and 7 of the specification and β_2-agonists are treatable by the present invention. The specification provides support for the interaction between the β2ARs and β_2-agonists in airway diseases, and as it is well understood by persons skilled in the art that the administered β_2-agonists bind to the β2ARs to be effective therapeutically. The more β2ARs present in the cells of the subject's airway, the more binding of β_2-agonists. In view of these arguments, applicants maintain that the amended claims are supported by the specification.

Additionally, applicants have canceled subject matter from the pending claims that treat vascular diseases or administer the vector containing the β2AR gene to blood vessel endothelial or smooth muscle cells without prejudice or disclaimer at this time in a effort to expedite prosecution.

The Examiner states that there is no indication that studies in cultured cells and rats have been performed. Applicants herewith enclose a declaration under 37 C.F.R. §1.132 **(Exhibit 8)** by one of the inventors, Dr. Lawrence Cornett that provides evidence of expression of the β2ARs in the cells of rat lungs using the construct, the β2AR gene under the control of a CMV promoter, as disclosed in the specification. It is requested that the

Examiner consider the attached declaration and accompanying figures supporting the expression of β2ARs in cells of the rat lung.

In response to the Examiner comments regarding whether gene therapy has utility in treating human disease in general, and asthma in particular, applicants direct the Examiner to several successful studies. In March 2000, Children's Hospital in Philadelphia and Stanford University reported success in using gene therapy to treat hemophilia B in 3 patients. The gene encoding Factor IX was delivered with AAV.

More recently, an Italian group reported correction of severe combined immunodeficieny (SCID) by gene therapy (Aiuti et al., Science 296:2410-2413, (2002)) **(Exhibit 9)**. Stem cells from 2 SCID children (remember the "bubble boy", this is the syndrome) were infected with a retrovirus carrying a normal copy of the adenine deaminase (ADA) gene. SCID is due to a defective ADA gene. The transformed stem cells were reintroduced into the patients.

In regard to the Examiner's citation of the review article by Phil Factor (Molecular Therapy 4:515-524) that discusses difficulties in treating asthma with gene therapy, applicants respectfully submit that the Examiner has not fully consider the entire Factor publication. For example, if one reads a little further in this article (sentence bridging columns 1 and 2 of page 518), the author states "Preliminary data from the author's laboratory indicate that adenoviral mediated overexpression of beta2-adrenergic receptor in the bronchial epithelium of normal mice attenuates methacholine-induced bronchospasm by increasing sensitivity to endogeneous catecholamines". This statement clearly supports the presently pending claims as the intention of the present invention is to overexpress β2ARs in cells of the airways. Applicants submit that Factor results support the enablement of the pending claims.

The Examiner states that Factor suggests that liposome-mediated gene therapy provides modest transduction efficiency. Applicants invention is directed to providing a vehicle to administer the β2AR containing AAV vector to the cells of the subjects airways, and thereby increase the β2ARs in the airway cells from the endogenous levels. Any transduction method whereby an increase in β2ARs in these cells occurs will be useful in treatment of a subject with airway diseases. It is not required that applicants' claimed

method be the most efficient method whereby the airway cells are transduced. All that is necessary is that the method is functional and liposomes are known vehicles for mediating gene transfer. Additionally, Factor does not state that liposome-mediated gene transfer is not operative. Applicants also note that the Kawahira publications disclose animal model experiments that are relied upon by the Examiner in the rejections based on lack of novelty and obviousness utilized a liposome-mediated delivery system. Further, these publications' working examples were interpreted as transfecting and expressing β2ARs in at least one cell. Also Demoly cited by the Examiner in support of his position is a review article that merely speculates on tools for the development of gene therapy for asthma. No data is provided by his research group, and therefore this publication fails to support the Examiner's position. In view of these arguments, it is requested that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102 and 103

Bretin

Claims 30-34 and 37 are rejected as allegedly anticipated by Bretin *et al.* ("Bretin") because Bretin discloses a plasmid vector comprising a transgene encoding a fusion polypeptide comprising a β2AR and an α subunit of adenylyl cyclase-stimulatory G protein, and operably linked to a CMV promoter used to transfect tissue culture cells. The claims have been amended to recite that the pharmaceutical composition containing the β2AR gene is suitable for airway delivery which imparts this feature to the claimed composition. It is requested that this rejection be withdrawn as Bretin does not disclose such a composition for airway delivery .

Kawahira *et al.* - 1999

Claims 30, 32, 33 and 37 are rejected as allegedly anticipated by Kawahira *et al.*-*1999* ("Kawahira-99") because this publication discloses a method of providing a β2AR to the heart via the cardiac myocytes to enhance cardiac function by intracornonary infusion of HVJ liposome comprising a vector containing a β2AR operably linked to a CMV promoter

followed by the administration of a β_2-agonist. The claims have been amended to recite that the pharmaceutical composition containing the β2AR gene is suitable for airway delivery. It is requested that this rejection be withdrawn as Kawahira-99 does not disclose such a composition.

Claims 1, 4, 8-10, 12, 15 and 19-22 are rejected as allegedly obvious over Kawahira-99 because it would have been obvious to one of skill in the art to practice the Kawahira method for improving cardiac function in a failing human heart. The Examiner contends that the working example in Kawahira-99 provides a reasonable expectation of success in at least one of the cells as recited in the claims of the present invention. Applicants respectfully traverse this rejection but in an effort to expedite prosecution and as suggested by the Examiner, the rejected claims have been amended to recite that the β2AR gene containing vector has been administered via airway treatment. In view the comments and the claims amendments, it is requested that this rejection be withdrawn.

Kawahira *et al.* - 1998

Claims 30, 32, 33 and 37 are rejected as allegedly anticipated by Kawahira *et al.*-*1999* ("Kawahira-98") because this publication discloses the development of a method of providing a β2AR to the heart via the cardiac myocytes to enhance cardiac function by intracornonary infusion of HVJ liposome comprising a vector containing a β2AR and operably linked to a CMV promoter followed by the administration of a β_2-agonist. The claims have been amended to recite that the pharmaceutical composition containing the β2AR gene is suitable for airway delivery. It is requested that this rejection be withdrawn as Kawahira-98 does not disclose such a composition.

Claims 1, 4, 8-10, 12, 15 and 19-22 are rejected as allegedly obvious over Kawahira-98 because it would have been obvious to one of skill in the art to practice the Kawahira method for improving cardiac function in a failing human heart. The Examiner contends that the working example in Kawahira-98 provides a reasonable expectation of success in at least one of the cells as recited in the claims of the present invention. Applicants respectfully traverse this rejection and in an effort to expedite prosecution and as

suggested by the Examiner, the rejected claims have been amended to recite that the β2AR gene containing vector has been administered via airway treatment. In view the comments and the claims amendments, it is requested that this rejection be withdrawn.

Drazner

Claims 30, 32, 33 and 37 are rejected as allegedly anticipated by Drazner *et al.* ("Drazner") because this publication discloses an adenoviral vector containing a β2AR and operably linked to a CMV promoter. The claims have been amended to recite that the pharmaceutical composition containing the β2AR gene is suitable for airway delivery. It is requested that this rejection be withdrawn as Drazner does not disclose such a composition suitable for airway delivery, which imparts such a feature to the claimed composition. It is requested that this rejection be withdrawn.

Maurice *et al.*

Claims 1, 4, 8, 11, 15 and 19-22 are rejected as allegedly obvious over Maurice *et al.* ("Maurice") because it would have been obvious to one of skill in the art to practice the Maurice method for improving cardiac function in a failing human heart by intracoronary perfusion of an adenoviral vector containing the β2AR gene operably linked to a CMV promoter, followed by the delivery of a β_2-agonist. The Examiner contends that the working example in Maurice provides a reasonable expectation of success in at least one of the cells as recited in the claims of the present invention. Applicants respectfully traverse this rejection. In an effort to expedite prosecution and as suggested by the Examiner, the rejected claims have been amended to recite that the β2AR gene containing vector has been administered via airway treatment. In view the comments and the claims amendments, it is requested that this rejection be withdrawn.

Hammond in view of both Kawahira publications or Maurice

Claims 1, 3-5, 8, 10-13, 15-22, 30, 32, 33, 35, 37, 38 and 49 are rejected as allegedly obvious over Hammond *et al.* ("Hammond") as evidenced by Ping *et al.* ("Ping")

in view of any one of Kawahira *et al.*- 1999 ("Kawahira-99"), Kawahira *et al.*- 1998 ("Kawahira-98") or Maurice *et al.* ("Maurice"). Hammond is applied as teaching a method of gene therapy for improving cardiac function in treatment of congestive heart failure in humans by delivering a vector containing a transgene encoding a β2AR operably linked to a promoter (inducible, tissue-specific or a CMV promoter) to coronary blood vessels. The Examiner states that Hammond discloses preferably using other genes than β2AR. The two Kawahira publications and Maurice are applied as discussed above. The Examiner argues that the claimed invention is obvious over the method of Hammond to treat congestive heart failure in combination with the disclosed animal modes of Kawahira publications and Maurice. In an effort to expedite prosecution and as suggested by the Examiner, the rejected claims have been amended to recite that the β2AR gene containing vector has been administered via airway treatment. In view the comments and the claims amendments, it is requested that this rejection be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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MARKED UP VERSION OF CLAIMS

1. (Amended) A method for providing a β_2-adrenergic receptor (β_2AR) to airway epithelial cells, airway smooth muscle cells[, blood vessel endothelial cells, blood vessel smooth muscle cells] or a combination thereof, of a human subject comprising:

(a) administering **via airway treatment** to at least one cell type selected from the group consisting of airway epithelial cells, airway smooth muscle cells[, blood vessel endothelial cells,] and [blood vessel smooth muscle cells] **a combination thereof** of a human subject, a first composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one of said cells of said subject, under conditions whereby the DNA sequence encoding said β_2AR is expressed in at least one of said cells.

3. (Amended) The method of claims 1, wherein said promoter is an inducible promoter, and said method further comprises:

(b) administering **via airway treatment** a second composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells.

4. (Amended) The method of claims 1, wherein said method further comprises:

(b) administering **via airway treatment** a second composition comprising at least one β_2-adrenergic agonist to said cells of said subject.

5. (Amended) The method of claim 4, wherein said promoter is an inducible promoter, said method further comprises:

(c) administering **via airway treatment** a third composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells.

8. (Amended) A method of treating a human subject having airway [or vascular] disease comprising:

(a) administering **via airway treatment** to at least one cell type selected from the group consisting of airway epithelial cells, airway smooth muscle cells**[**, blood vessel endothelial cells,**]** and **[**blood vessel smooth muscle cells**]** **and a combination thereof**, a first composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one of said cells of said subject, under conditions whereby the DNA sequence encoding said β_2AR is expressed in at least one of said cells; and

(b) administering **via airway treatment** a second composition comprising at least one β_2-adrenergic agonist into said cells of said subject.

9. (Amended) The method of claim 8 wherein said **[**epithelial**]** cell is an airway epithelial cell.

18. (Amended) The method of claim 17, wherein said method further comprises:

(c) administering **via airway treatment** a composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells.

20. (Amended) The method of claims 1, wherein said first composition further comprises a pharmaceutically acceptable carrier for aerosol delivery **[**or for intravenous delivery**]**.

30. (Amended) A pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways **[**or blood vessels**]** of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells**[**, blood vessel endothelial cells**]** and **[**blood vessel smooth muscle cells**]** **a combination thereof**; and a pharmaceutically acceptable carrier**, wherein said pharmaceutical composition is suitable for airway delivery to said subject**.

32. (Amended) The pharmaceutical composition of claims 30, wherein said pharmaceutical composition is suitable for aerosol delivery [or intravenous delivery].

33. (Amended) A kit for the treatment of a human subject having airway [or vascular] disease comprising:

(a) a first pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways [or blood vessels] of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells[, blood vessel endothelial cells] and [blood vessel smooth muscle cells] **a combination thereof**; and a pharmaceutically acceptable carrier**, wherein said first pharmaceutical composition is suitable for airway delivery to said subject**; and

(b) a second pharmaceutical composition comprising at least one β_2-adrenergic agonist and a pharmaceutically acceptable carrier**, wherein said second pharmaceutical composition is suitable for airway delivery to said subject**.

35. (Amended) The kit of claim 33, , wherein said promoter is an inducible promoter, said kit further comprises:

(c) a third pharmaceutical composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells**, wherein said third pharmaceutical composition is suitable for airway delivery to said subject**.

38. (Amended) A kit for the treatment of a human subject having airway [or vascular] disease comprising:

(a) a first pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways [or blood vessels] of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells[, blood vessel endothelial cells] and [blood vessel smooth muscle cells] **a combination thereof**; and a pharmaceutically acceptable carrier; and

(b) a second pharmaceutical composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells**, wherein said first and second pharmaceutical compositions are suitable for airway delivery to said subject**.

44. (Amended) The method of claim 3, wherein said promoter **is a mammalian cell specific promoter** [is] selected from the group consisting of an epithelial cell specific promoter, an endothelial cell specific promoter and a smooth muscle cell specific promoter.

45. (Amended) The method of claim 5, wherein said promoter **is a mammalian cell specific promoter** [is] selected from the group consisting of an epithelial cell specific promoter, an endothelial cell specific promoter and a smooth muscle cell specific promoter.

46 (Amended) The pharmaceutical composition of claim 30, wherein said promoter **is a mammalian cell specific promoter** [is] selected from the group consisting of an epithelial cell specific promoter, an endothelial cell specific promoter and a smooth muscle cell specific promoter.

47. (Amended) The kit of claim 35, wherein said promoter **is a mammalian cell specific promoter** [is] selected from the group consisting of an epithelial cell specific promoter, an endothelial cell specific promoter and a smooth muscle cell specific promoter.

48. (Amended) The kit of claim 38, wherein said promoter **is a mammalian cell specific promoter** [is] selected from the group consisting of an epithelial cell specific promoter, an endothelial cell specific promoter and a smooth muscle cell specific promoter.

49. (Amended) A kit for the treatment of a human subject having airway [or vascular] disease comprising:

a first pharmaceutical composition comprising a vector comprising a DNA sequence encoding a β_2AR operably linked to a promoter that is functional in at least one cell of the airways [or blood vessels] of a human subject, wherein said cell is selected from the group consisting of an airway epithelial cells, airway smooth muscle cells[, blood vessel

endothelial cells] and [blood vessel smooth muscle cells] **a combination thereof**; and a pharmaceutically acceptable carrier;

a second pharmaceutical composition comprising at least one β_2-adrenergic agonist and a pharmaceutically acceptable carrier; and

a third pharmaceutical composition comprising a hormone or pharmacological agent that induces said promoter to express said β_2AR in at least one of said cells**, wherein said first, second and third pharmaceutical compositions are suitable for airway delivery to said subject**.

50. (Amended) The kit of claim 49, wherein said promoter **is a mammalian cell specific promoter** [is] selected from the group consisting of an epithelial cell specific promoter, an endothelial cell specific promoter and a smooth muscle cell specific promoter.